Literature Report III

Total Synthesis of (-)-Neocucurbol C Enabled by Pattern Recognition and MHAT Cyclization

Reporter: Xin-Yang Li

Checker: Kai Xue

Date: 2025-09-08

Zhong, L.; Zhen, J.; Adibekian, A.; Dai, M. *J. Am. Chem. Soc*. **2025**, *147*, 28589-28594

CV of Prof. Mingji Dai

Background:

- **1998-2002** B.S., Peking University
- **2002-2004** Research Assistant, Peking University
- **2004-2009** Ph.D., Columbia University
- **2009-2012** Postdoctoral Fellow, Harvard University
- **2012-2020** Assistant Professor, Associate Professor, Purdue University
- **2020-2022** Professor, Purdue University
- **2022-Now** Professor, Emory University

Research Field:

- Total Syntheses of Natural and Unnatural Molecules
- Synthetic Methodology

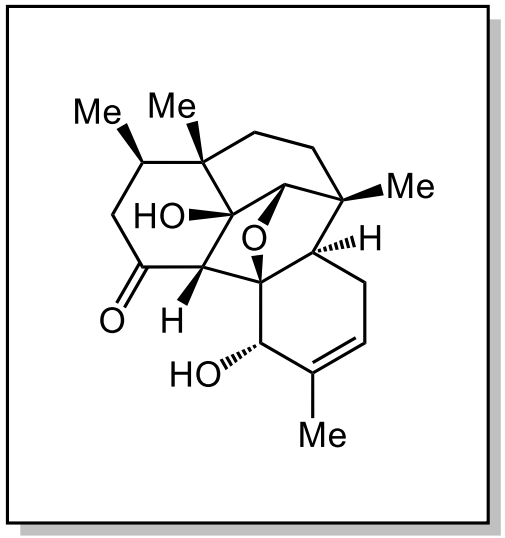
Contents

1 Introduction

2 Total Synthesis of (-)-Neocucurbol C

3 Summary

Introduction



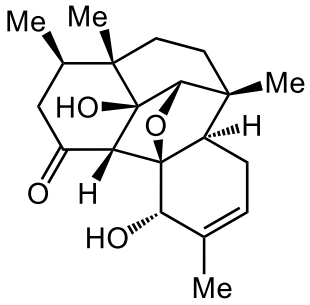
(-)-Neocucurbol C

***Neocucurbitaria unguis-hominis* FS685**

- It was isolated deep-sea sediment sample by Zhang in 2022
- It contains a 6/6/5/5/6 polycyclic skeleton and nine stereocenters
- Bioassays show that it exhibited anticancer activity

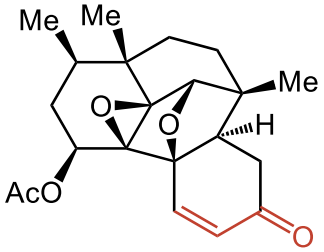
Hu, J.; Zhang, W. *J. Nat. Prod.* **2022**, *85,* 1967-1975.

Retrosynthetic Analysis



Neocucurbol C (**3**)

FGI



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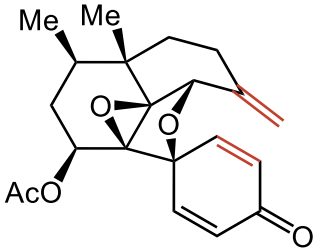
MHAT

cyclization



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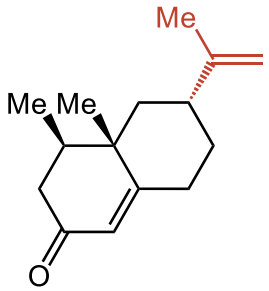
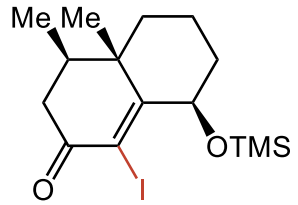
oxidative dearomatization



(+)-nootkatone (**13**)

C-C cleavage



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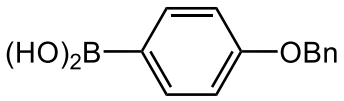
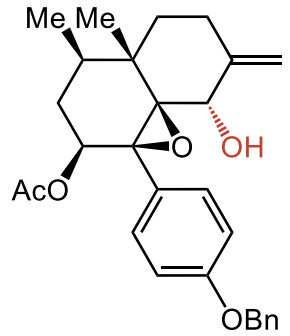
cross coupling





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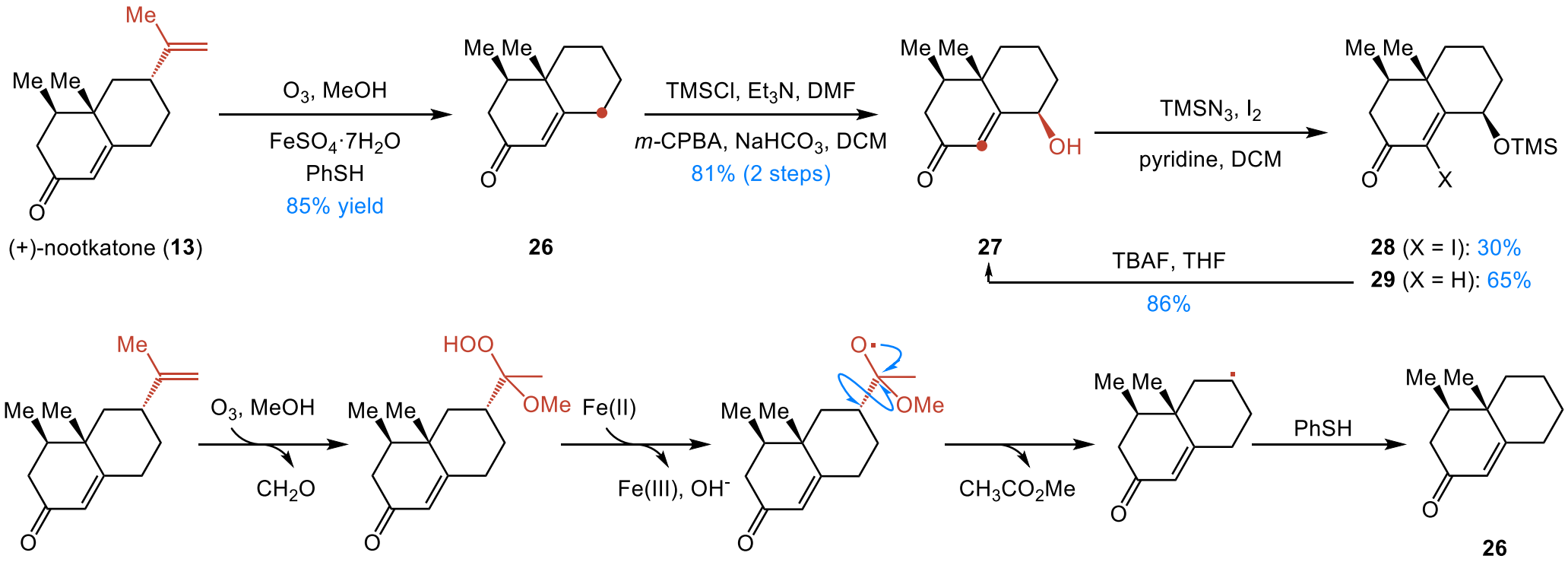
Stage 1: Synthesis of Compound 28



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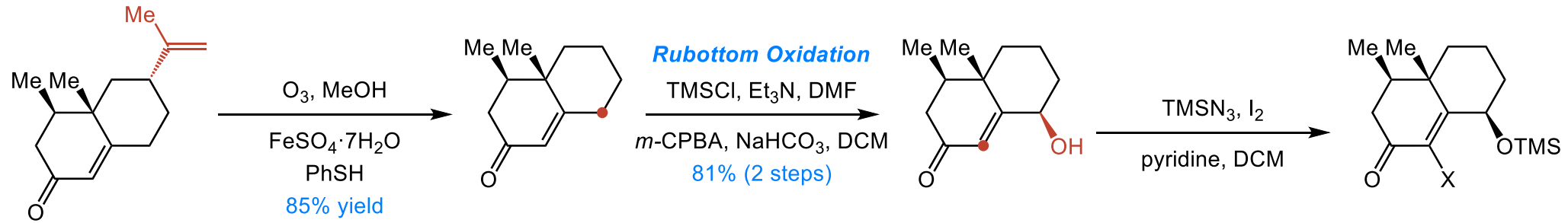

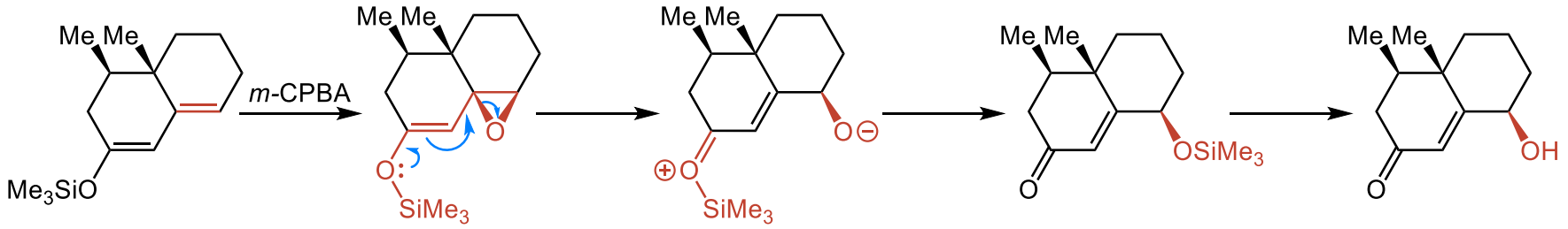

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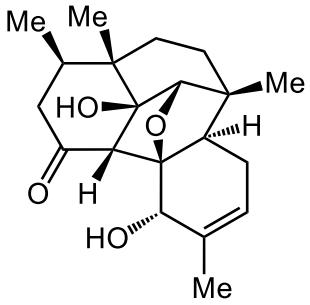

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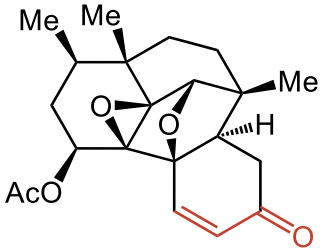

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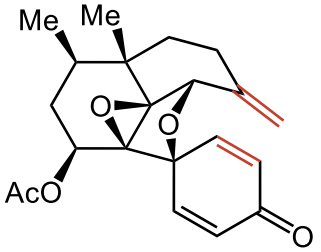
MHAT

cyclization



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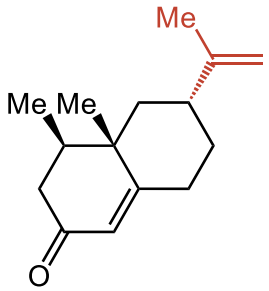

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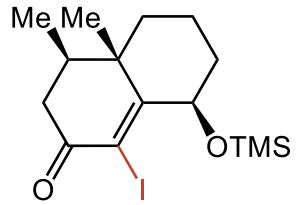

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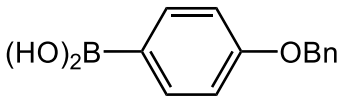
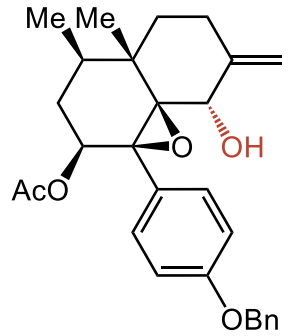
cross coupling





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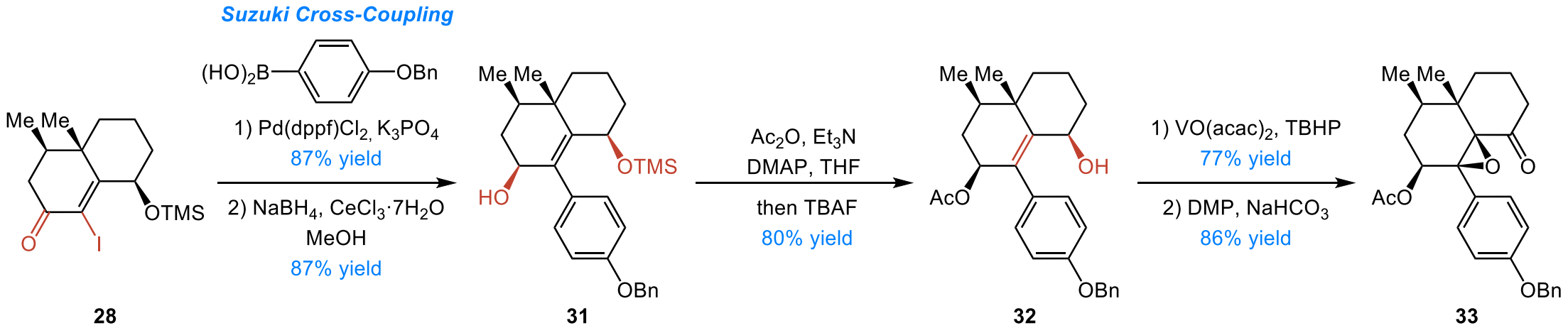
Stage 2: Synthesis of Compound 36



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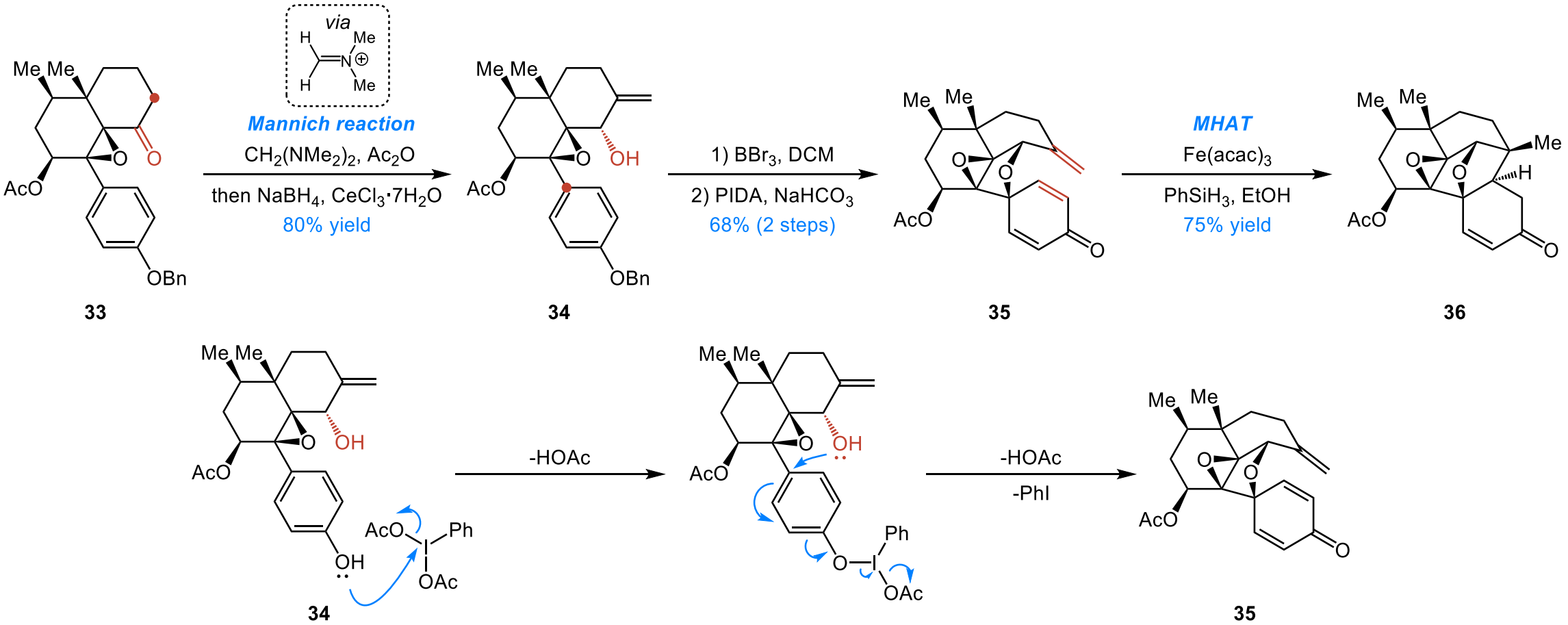

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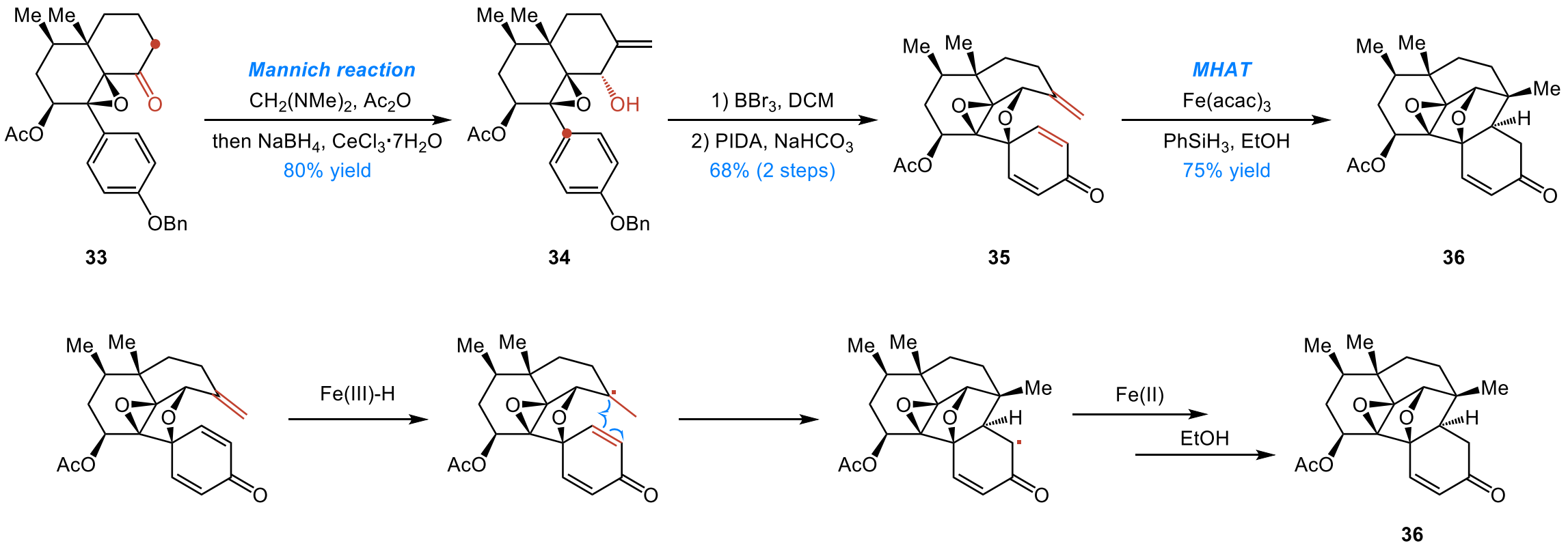

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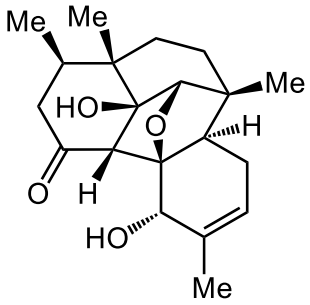

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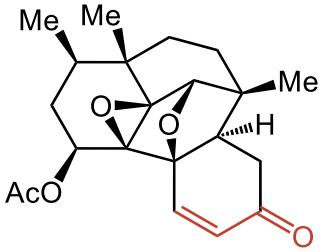

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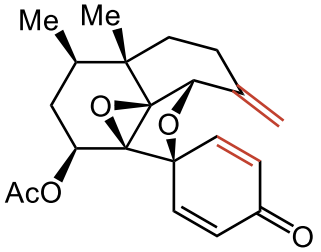

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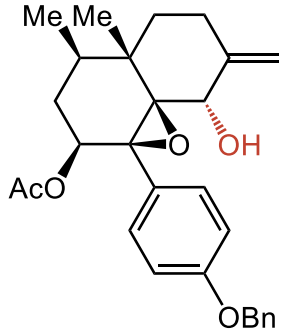

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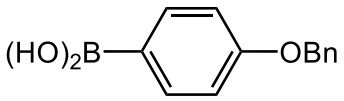

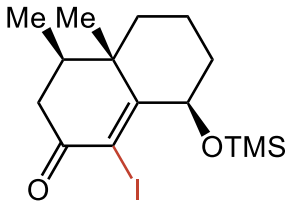

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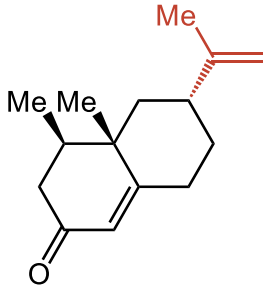
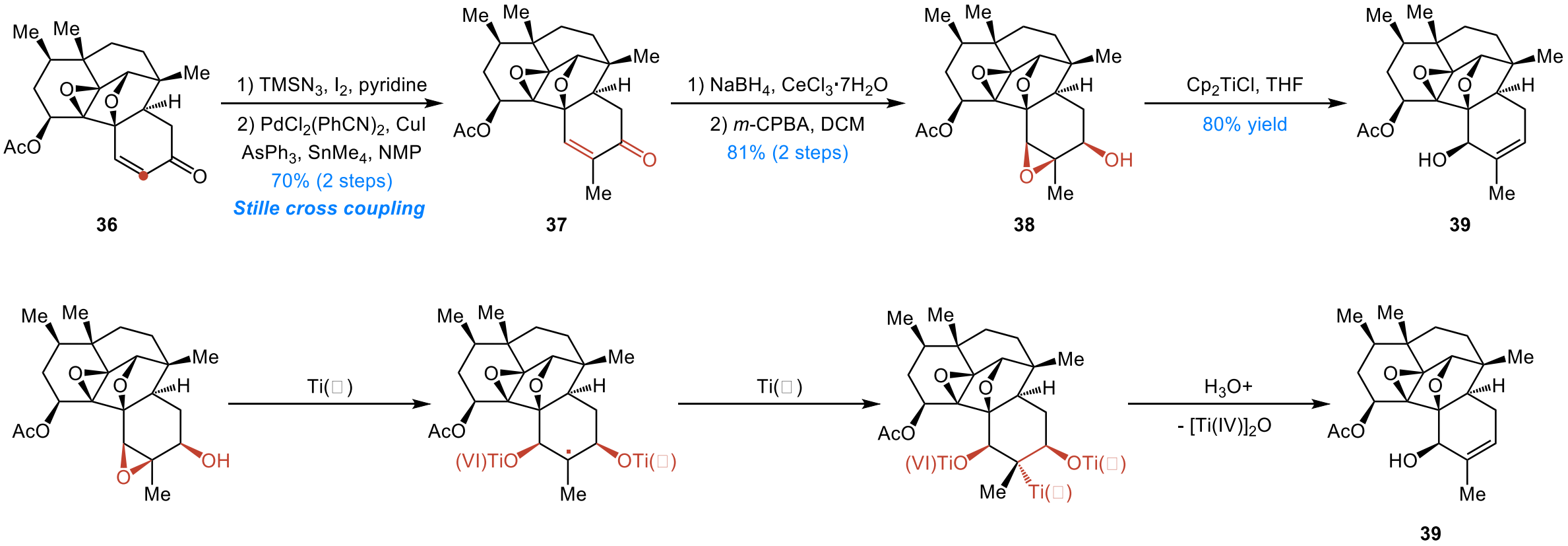
C-C cleavage



(+)-nootkatone (**13**)

Stage 3: Synthesis of Compound Neocucurbol C



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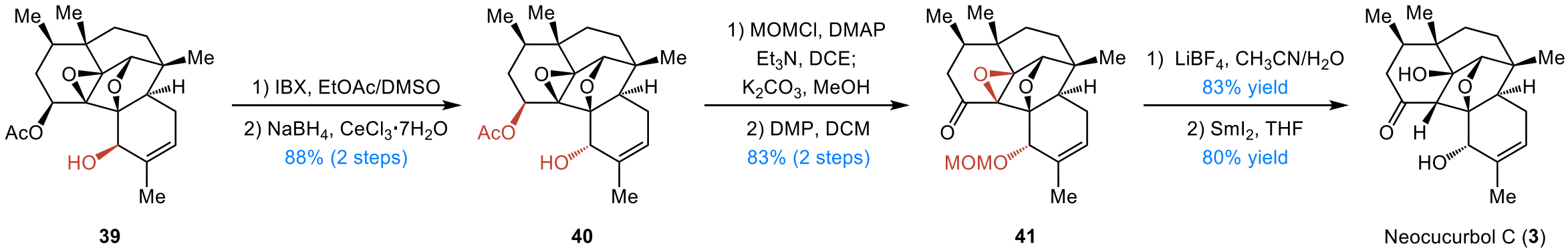
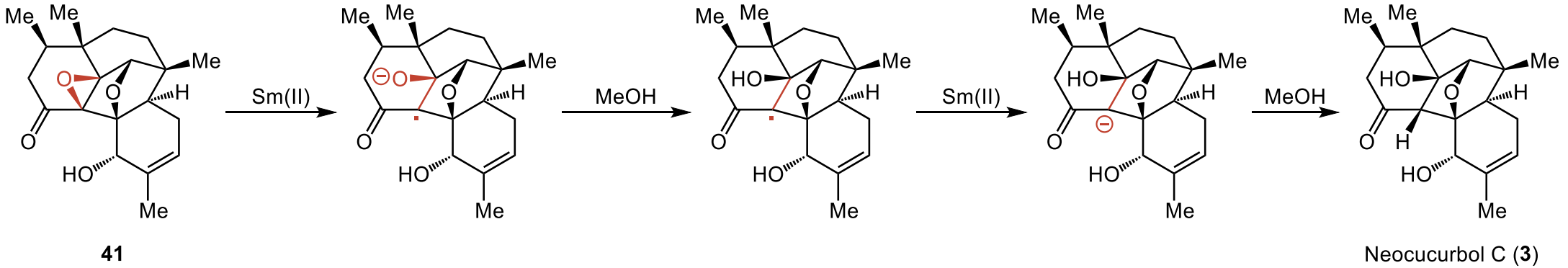
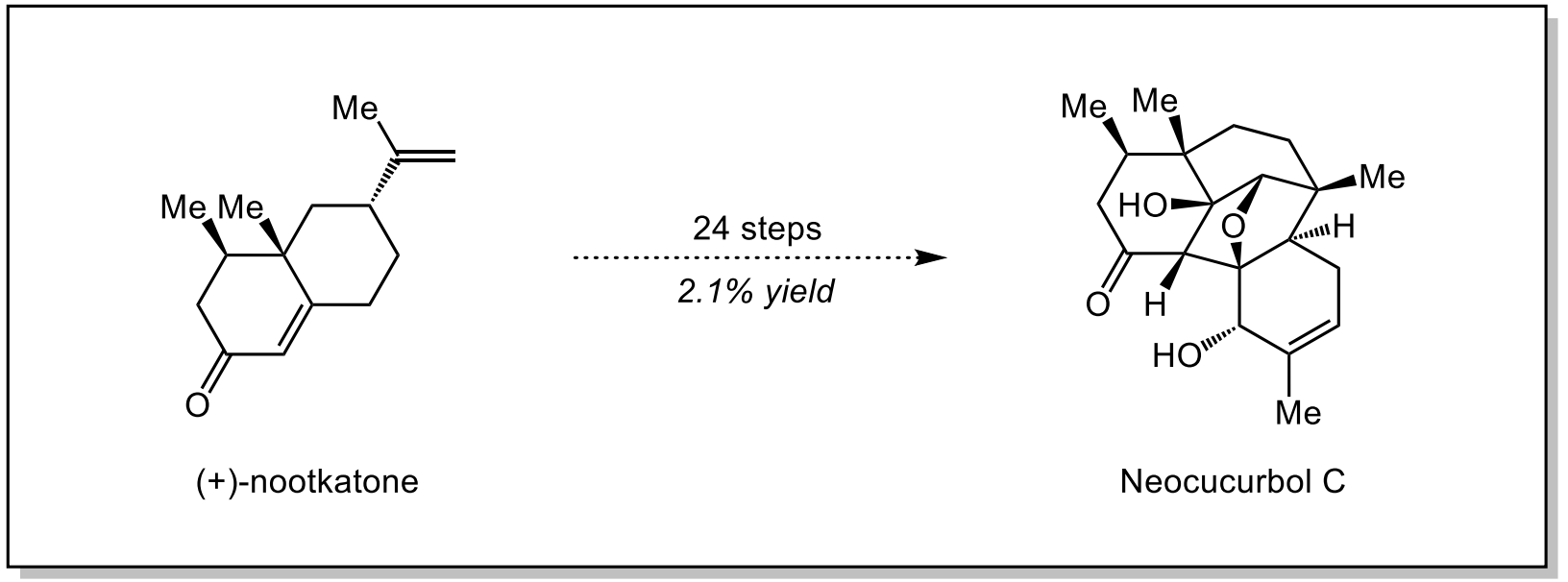




Summary



- Removal of nootkatone's extra isopropenyl group via Kwon's hydrodealkenylative bond fragmentation.
- Construction of aromatic ring and key oxa-bridge through Suzuki-Miyaura cross-coupling and oxidative dearomatization cyclization.
- Completion of the entire framework by MHAT-initiated reductive radical cyclization.

Writing Strategy

First paragraph

Source

Structure

Biosynthetic Pathway Prediction

- The neocucurbols are produced by *Neocucurbitaria unguis-hominis* FS685, a strain originating from a deep-sea sediment sample. They were isolated by Zhang and co-workers in 2022 and characterized as novel phomactin diterpenes.
- Among them, neocucurbols A−D represent the first phomactin family members with a complex and unprecedented 6/6/5/5/6 polycyclic skeleton. Three bridged ring systems (a bicyclo[5.3.1]undecane, a bicyclo[3.3.1]nonane, and an oxabicyclo-[2.2.1]heptane) and eight or nine stereocenters are embedded in their remarkable framework. In addition, four other neocucurbols (E−H) featuring a unique 6/8/6 tricyclic carbon skeleton were identified from the same extract.
- Biosynthetically, the neocucurbols are believed to derive from geranylgeranyl pyrophosphate by going through phomacta- triene.....

Writing Strategy

➢ **Last paragraph**

Summary

↓

Committed Steps

↓

Prospect

- In summary, we completed the first total synthesis of neocucurbol C in 24 steps.
- Pattern-recognition analysis enabled us to identify (+)-nootkatone as a readily available starting material, the unnecessary isopropenyl group of which was trimmed off with Kwon's hydrodealkenylative bond fragmentation. An aromatic starting material was used as the E ring precursor and appended on the AB ring system with Suzuki−Miyaura cross coupling. The most connected oxabicyclo[2.2.1]heptane ring was subsequently constructed with an oxidative dearomatization, followed by a MHAT reductive cyclization.....
- While the following peripheral decoration took a longer sequence than ideal, it produced synthetic intermediates with the neocucurbol skeleton for biological evaluation, from which compound 36 and its precursor 35 were identified to show promising anticancer activity and are worth further inves- tigation.....

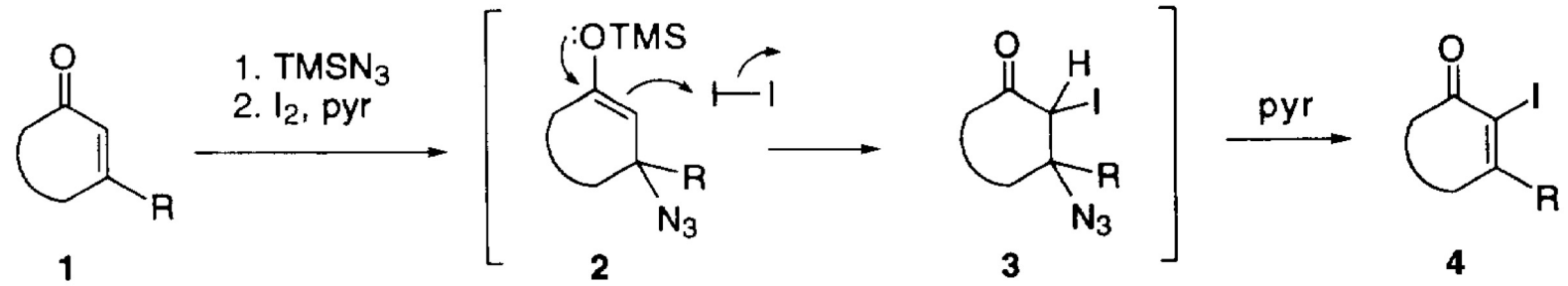
Representative Examples

- We next needed to migrate the oxygen functionality from C12 to C14, an issue resulting from moving the phenol from the ortho to para position to enable a successful oxidative dearomatization and MHAT cyclization. (*n.* 去芳构化)
- With **36** in hand, peripheral decoration was needed to introduce one more methyl group and adjust the oxidation state. Installation of the C13 methyl group was accomplished by α-iododination followed by Stille cross coupling. (外围修饰(在分子核心骨架构建完成后，对侧链或非核心结构进行的官能团修饰))
- In addition, the cytotoxicity evaluation of (−)-neocucurbol C and its synthetic intermediates against multiple cancer cell lines identified new lead compounds with promising anticancer activity for further development. (细胞毒性评价)

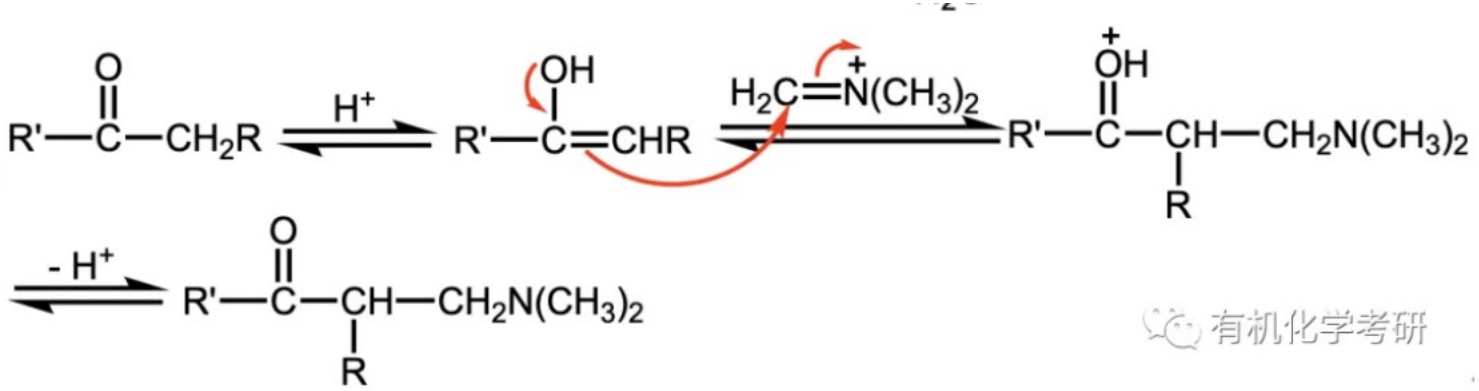
Acknowledgement

Thank You for Your Attention

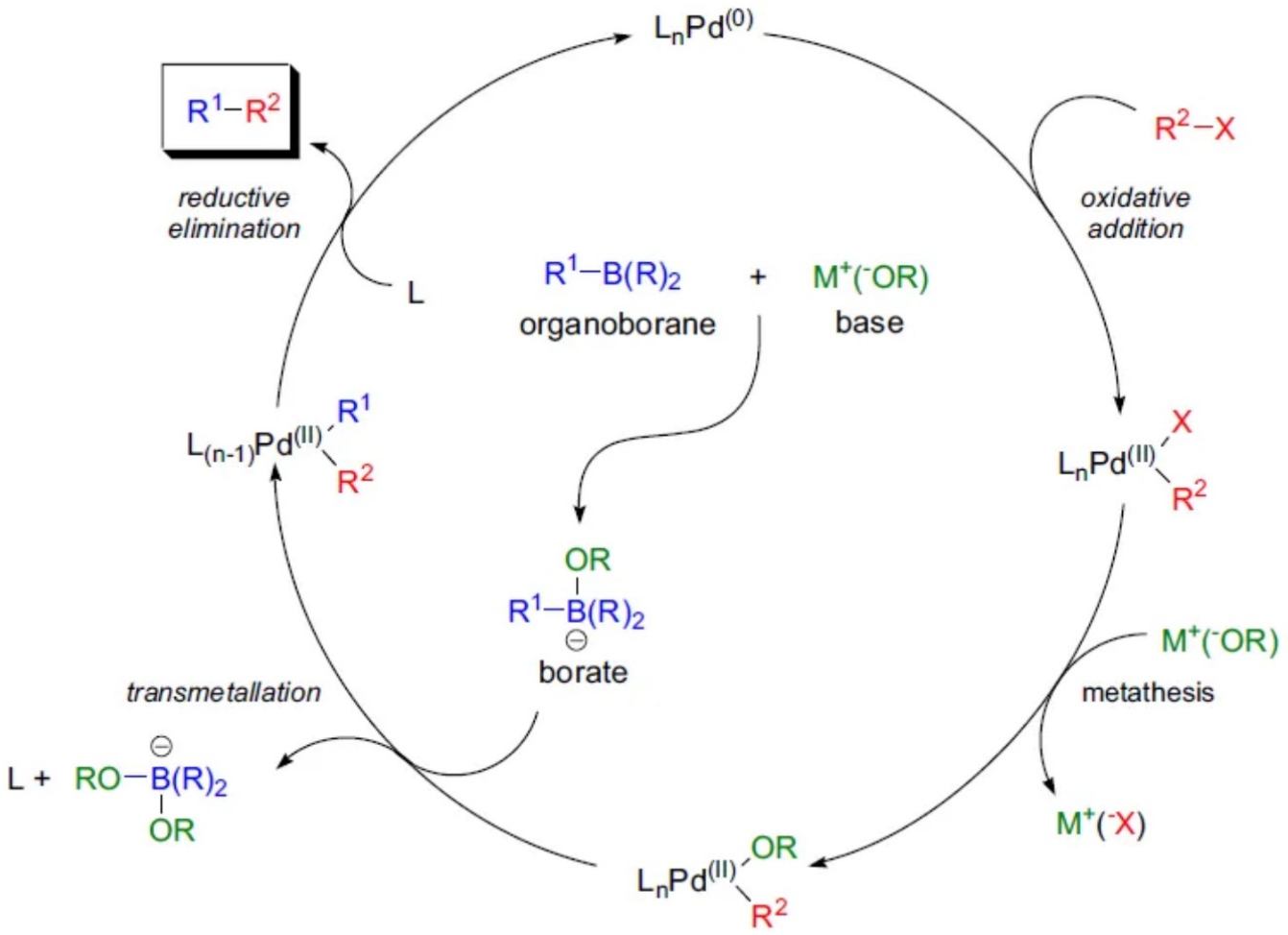
Synthesis of 28



Synthesis of 34 ： mannich反应



Synthesis of 34 ： suzuki 偶联



Synthesis of 37 ： stille 偶联